Massachusetts Department of Public Health
State Laboratory Institute
Bureau of Communicable Disease Control
Bureau of Laboratory Sciences

Guidance for Clinicians and Laboratorians Regarding Avian Influenza A (H5N1)

TABLE OF CONTENTS

OVERVIEW

Outbreaks of highly pathogenic avian influenza (HPAI) type A H5N1 with significant domestic bird mortality have been documented in Eurasia and Africa. Updated information can be found on the World Organization for Animal Health website at: http://www.oie.int/eng/en_index.htm.

Of the laboratory-confirmed cases of avian influenza A (H5N1) in humans reported in Asia, Eurasia, and Africa the mortality rate continues to be approximately 50%. Although there has been no evidence of sustained, efficient person-to-person transmission, there are a few clusters of limited, probable person-to-person transmission. Updates can be found on the World Health Organization's (WHO) website: http://www.who.int/csr/disease/avian_influenza/country/en/. According to the WHO, the current H5N1 activity represents a "pandemic alert period in phase 3" defined by human infection(s) with a new subtype but no human-to-human spread or at most rare instances of spread to a close contact.

The Massachusetts Department of Public Health (MDPH) and the Association of Public Health Laboratories (APHL), Centers for Disease Control and Prevention (CDC) and other federal agencies have been working to provide recommendations and guidance related to: 1) surveillance of suspect cases of avian influenza, 2) laboratory confirmation using rapid molecular diagnostic testing specific for novel influenza subtypes, 3) control measures and precautions for patients and contacts, and 4) treatment and prophylaxis.

CLINICAL PRESENTATION

Most patients with influenza A (H5N1) infection have initial symptoms of high fever (typically a temperature of more than 38°C) and an influenza-like illness with upper and lower respiratory tract symptoms. Symptoms found in at least 50% of H5N1 hospitalized individuals include fever, cough, dyspnea, rhinorrhea and diarrhea. Sputum production is variable and sometimes bloody. Almost all patients have clinically apparent pneumonia. Progression to respiratory failure has been associated with diffuse, bilateral infiltrates and manifestations of the acute respiratory distress syndrome (ARDS).

INCUBATION VERSUS INFECTIOUS PERIODS

The **incubation period** of avian influenza A (H5N1) in humans may be longer than that with infection due to human influenza viruses. Incubation periods have generally been 2 to 5 days, but they have been as long as 8 to 17 days. For disease control purposes, a 10-day incubation period is currently being used.

The **infectious period** for avian influenza A (H5N1) is longer than that for other human influenzas. Patients should be considered infectious for 14 days after onset of symptoms. However, the period of viral shedding may be longer in children less than 12 years of age and those who are immunosuppressed.

SURVEILLANCE AND REPORTING

The CDC is urging providers to carry out enhanced surveillance in travelers with severe unexplained respiratory illness returning from H5N1-affected countries. For an updated listing of H5N1-affected countries, see the World Organization of Animal Health (OIE) website at http://www.oie.int/eng/en_index.htm and the WHO website at http://www.who.int/csr/disease/avian_influenza/en/.

1. **Patients who *should* be evaluated and tested for avian influenza (H5N1) based on the following high-risk criteria:**
   - ❑ Have illness that requires hospitalization or is fatal; **AND**
   - ❑ has or had a documented temperature of ≥38°C (≥100.4° F); **AND**
   - ❑ has radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness for which an alternate diagnosis has not been established; **AND**
   - ❑ has at least one of the following potential exposures within 10 days of symptom onset:

   A) History of travel to a country with influenza H5N1 documented in poultry, wild birds, and/or humans, **AND** had **at least one** of the following:
   - direct contact with (e.g., touching) sick or dead domestic poultry;
   - direct contact with surfaces contaminated with poultry droppings;
   - consumption of raw or incompletely cooked poultry or poultry products;
   - direct contact with sick or dead wild birds suspected or confirmed to have influenza H5N1;
   - close contact (approach within 1 meter [approx. 3 feet]) of a person who was hospitalized or died due to a severe unexplained respiratory illness;

   B) Close contact (approach within 1 meter [approx. 3 feet]) of an ill patient who was confirmed or suspected to have H5N1;

   C) Worked with live influenza H5N1 virus in a laboratory.

Immediately notify your Local Board of Health, and the Massachusetts Department of Public Health (MDPH) at 617-983-6800 (24/7) and ask for the Immunization Epidemiologist to REPORT patients who fit these criteria. Assistance with specimen collection, transport, and diagnostic testing will be provided as detailed below.

2. **Patients who should be *considered* for testing for avian influenza**
   Testing for avian influenza A (H5N1) should be considered on a case-by-case basis in consultation with MDPH epidemiologists for hospitalized or ambulatory patients with:
   - mild or atypical disease‡ (hospitalized or ambulatory) who has one of the exposures listed

above (criteria A, B, or C); **OR**

- A patient with severe or fatal respiratory disease whose epidemiological information is uncertain, unavailable, or otherwise suspicious but does not meet the criteria above (examples include: a returned traveler from an influenza H5N1-affected country whose exposures are unclear or suspicious, a person who had contact with sick or well-appearing poultry, etc.)

‡ For example, a patient with respiratory illness and fever who does not require hospitalization, or a patient with significant neurologic or gastrointestinal symptoms in the absence of respiratory disease.

SPECIMEN COLLECTION AND DIAGNOSTIC TESTING

HPAI influenza A (subtype H5 or H7) viruses are regulated as U.S. Department of Agriculture (USDA) Select Agents, and viral cultures **must** be handled in biosafety level (BSL)-3 enhanced laboratory settings with Select Agent certification. Therefore, **respiratory virus cultures should not be performed on patients with possible infection with an influenza A H5 or H7 in most clinical laboratories and such cultures should not be ordered for patients suspected of having H5N1 infection.**

All specimens should be collected using appropriate precautions (see section on **Control Measures, Precautions in Health-care Facilities** for further guidance). Contact an MDPH immunization epidemiologist **immediately** at 617- 983-6800 (24/7) when collecting clinical specimens on suspect cases of avian influenza. The epidemiologist will provide additional information about sample collection and arrange for transportation to the State Laboratory Institute (SLI) for rapid diagnostic molecular testing. SLI is approved by the CDC's Laboratory Response Network (LRN) and Influenza Branch to perform reference level testing by real-time detection PCR (RTD-PCR). These assays are specific for influenza A/H5 (Asian lineage), as well as, other avian and seasonal influenza subtypes. In a pre-pandemic stage, where suspect specimens are ruled out for influenza novel subtypes H5 or H7 by RTD-PCR, SLI will perform routine viral isolation and confirmatory identification of influenza subtypes by hemagglutination inhibition (HAI) and immunofluorescence assay (IFA) tests.

A positive RTD-PCR test result for a novel influenza strain (H5 or H7) is currently considered presumptive identification, and confirmatory testing by multiple methods will be required for the first cases detected in the U.S. Because negative tests cannot rule out avian influenza in cases with a high index of suspicion, molecular testing should also be repeated on multiple samples over multiple days.

A. Collection of Appropriate Clinical Specimens for Diagnostic Testing

Refer to the SLI's Respiratory Virus Specimen Collection Instructions (form #SI-VI-1-06) found on the MDPH website (http://www.mass.gov/dph/bls/generalform.pdf). Please note: detection of influenza H5N1 is more likely from specimens collected within the first three days of illness onset. In order to increase the ability to detect virus, we recommend **multiple** sample types be obtained over **several days** from the same patient. Specifically, the **minimum specimen requirement for influenza A (H5N1) testing** is an oropharyngeal swab. In general, for most influenza testing, a nasopharyngeal swab OR wash OR aspirate is useful. This may be obtained at the same time as the oropharyngeal swab. Lower respiratory tract specimens such as sputum, when available, and bronchoalveolar (BAL), tracheal aspirate, or pleural fluid tap, if obtained, should also be sent to SLI for testing.

Specimen details for influenza (H5N1) testing:

1. **Oropharyngeal swab specimen (throat swab) – preferred sample type**
   Collect oropharyngeal specimens by swabbing the posterior pharynx and tonsillar pillars. This type of sample currently yields the highest concentration of influenza A (H5N1) virus. **NOTE**- Swab specimens should be collected only on swabs with Dacron®, rayon, or flocked tips and an aluminum or plastic

shaft. Swabs with calcium alginate or cotton tips with wooden shafts are unacceptable and may result in specimen rejection. Specimens should be placed in 3 mL viral transport medium (VTM) at 4°C immediately after collection. Place at 4°C until shipped.

2. Nasopharygeal (NP) aspirate/wash or swab

Instill 1.0-1.5 ml of nonbacteriostatic saline (pH 7.0) into one nostril. Flush a plastic catheter or tubing with 2-3 ml of saline. Insert the tubing into the nostril parallel to the palate. Aspirate the nasopharyngeal secretions and transfer to a sterile vial with an external cap and internal O-ring seal, if available. Secure tube and seal cap with Parafilm. For nasopharygeal swabs, insert the swab into the nostril parallel to the palate. **NOTE**- Dacron®, rayon or flocked NP swabs are acceptable. Rotate the swab slightly several times to dislodge the columnar epithelial cells and then quickly remove the swab. Place the swab into 3 ml of VTM at 4°C immediately after collection. Place specimen(s) at 4°C until shipped.

3. Lower respiratory tract specimens

If a patient is intubated, take a tracheal aspirate or collect a sample during bronchoalveolar lavage. Specimens should be placed in sterile vials with external caps and internal O-rings seals, if available. Secure tubes and seal caps with Parafilm. Due to aerosol-generating risk during these procedures, take appropriate infection control precautions including the use of gloves, gown, goggles, or face shield, and a N-95 rated filter or higher level of respiratory protection. Place at 4°C until shipped.

If a patient is not intubated, educate the patient about the difference between sputum and oral secretions. Have the patient rinse their mouth with water and then expectorate deep cough sputum directly into a sterile collection cup. Place at 4°C until shipped.

4. Blood

Collect 5-10 ml of whole blood in a serum separator tube. Allow to clot, centrifuge briefly and transfer resulting serum to vials with external caps and O-rings. Secure tubes and seal caps with Parafilm. If possible, collect an acute phase serum sample ≤7 days after symptom onset and convalescent sample after 3-4 weeks. Single serum samples can be collected ≥14 days after symptom onset. If sample is to be used for viral RNA detection, then blood serum or plasma should be collected 7-9 days after symptom onset. Ideally, the first specimen should be collected before antiviral therapy is begun, but treatment should not be delayed in order to collect the specimen. Place at 4°C until shipped.

5. Secondary specimens (not essential but may be useful if available)

Alternative specimens may include rectal swab (especially if patient exhibits diarrhea) or spinal fluid, if meningitis is suspected and a spinal tap is to be performed. Detailed WHO guidance can be found at: http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_ARO_2006_1/en/index.html.

6. Autopsy specimens

Autopsy specimens for RTD-PCR or immunohistochemical staining may be submitted in the case of unusual clinical presentation. **Note**- specimens to be tested by RTD-PCR should be submitted as fresh, frozen, and unfixed tissue. Submit both fresh and fixed tissue to the SLI if both assays are to be performed.

For RTD-PCR and virus isolation from fresh tissue, collect a deep endotracheal aspirate (2-3 mL). Additional appropriate samples would include fresh lung tissue (1-3 cm^3) or ~1 mL lung tissue aspirate from the margin of interstitial infiltration collected with an 18G needle and placed in VTM. Throat swabs, nasopharyngeal aspirates or stool samples may be collected if time, sampling materials and safety considerations permit.

For immunohistochemical staining, a minimum of 8 blocks (formalin-fixed, paraffin-embedded) or fixed tissue (10% neutral buffered formalin) representing samples from each of the autopsy sites listed below should be collected. These sites include:

- Central (hilar) lung with segmental bronchi
- Right and left primary bronchi
- Trachea (proximal and distal)
- Representative pulmonary parenchyma from right and left lung
- Additional tissue from major organs (dependent on clinical presentation). Specifically, for patients with suspected myocarditis or encephalitis, specimens should include myocardium (right and left ventricle) and CNS (cerebral cortex, basal ganglia, pons, medulla, and cerebellum).

B. Diagnostic Testing of Avian Influenza (H5N1) at the State Laboratory Institute

1. Molecular Testing

Upon approval by the MDPH Epidemiologist, SLI can perform two different molecular assays for rapidly identifying novel influenza from suspect patients within 4-6 hrs. These assays include 1) molecular influenza typing (A, B) and subtyping (H1, H3, H5, and H7) and 2) molecular influenza A/H5 (Asian lineage) on specimens from suspect patients. Currently, these reagents detect Asian H5N1 strains from both Clades 1 and 2; reagent modifications due to strain differences are incorporated into these reagents as needed by the CDC Influenza Branch. In a pre-pandemic stage, where suspect specimens are ruled out for influenza subtypes H5 or H7 by RTD-PCR, SLI will perform routine viral isolation and identification of influenza subtypes by hemagglutination inhibition (HAI) and immunofluorescence assay (IFA) tests. **Rapid molecular tests are available on a case-by-case basis** and physicians should contact MDPH at (617) 983-6800 (24/7) and ask for the Immunization Epidemiologist for consultation.

2. Viral Culture

Viral culture should not be performed on respiratory specimens from patients who meet the criteria for suspect H5N1 infection unless stringent laboratory conditions can be met. However, some original specimens may need to be submitted to the SLI's Virology Laboratory to be forwarded to CDC for inclusion in WHO surveillance based on genetic strain typing and antiviral resistance characterization.

3. Serologic Testing

Serologic testing for influenza H5N1-specific antibody, using appropriately timed specimens, will be considered if other influenza H5N1 diagnostic testing methods are unsuccessful (for example, due to delays in respiratory specimen collection). Paired serum specimens from the same patient are required for influenza H5N1 diagnosis: one sample should be tested within the first week of illness, and a second sample should be tested 3-4 weeks later. A demonstrated rise in the H5N1-specific antibody level is required for a diagnosis of H5N1 infection.

C. Testing in the Clinical Setting

1. Commercial Rapid Diagnostic Tests

Commercial rapid influenza antigen test results for the evaluation of suspected influenza H5N1 cases should be interpreted with caution. Clinicians should be aware that these tests have relatively low sensitivities, and a negative result would not exclude a diagnosis of influenza H5N1. In addition, a positive result does not distinguish between seasonal and avian influenza A viruses.

- **Patients with high index of suspicion:** In patients in whom you have a high index of suspicion (see **Surveillance** section above), point-of-care rapid testing should **not** be performed out of consideration of the safety of staff. Additionally, the sensitivity of rapid tests for influenza

H5N1 are low, so results from rapid testing should not be used to rule-out H5N1 infection. Patient testing should be done at the MA Department of Public Health.

- **Patients with a low index of suspicion:** In patients with a typical presentation of influenza-like illness and in whom you have a low suspicion of avian influenza A (H5N1), point-of-care rapid diagnostic testing can be helpful in ruling in influenza A as the etiology of respiratory illness. It should be emphasized that the sensitivity of these rapid diagnostic tests is lower than culture (~70%) and varies by test and specimen type. Interpretive criteria may be different depending on the level of influenza activity in the community. For specific interpretive criteria refer to the U.S. Department of Health and Human Services Pandemic Influenza Plan under the section "Information for Clinical Laboratory Directors" Section II pg. S2-25 (http://www.hhs.gov/pandemicflu/plan/sup2.html).

PACKAGING AND SHIPPING

Instructions for packaging and shipping routine or suspect influenza specimens for delivery to the State Laboratory Institute (SLI) can be found on the MDPH website under the Testing Methods section at: http://www.mass.gov/dph/cdc/epii/flu/pandemic_prov.htm. These documents include the Respiratory Virus Specimen Collection Instructions, MDPH specimen submission form, Division 6.2 Infectious Substances Shipping Guide, and an updated shipping label for the respiratory virus kit in compliance with new DOT, USPS and IATA shipping regulations.

It is **critical** that information pertaining to the patient's history including onset of symptoms, date of birth, history of contact with poultry, travel history, receipt of antiviral medication, influenza vaccination information (including type of influenza vaccine- e.g., inactivated versus live-attenuated, and date of vaccination) and previous laboratory results be included on the MDPH specimen submission form SS-SLI-1-05. For laboratory testing purposes, please state on the submission form that avian or novel influenza strain is suspected.

The specimen collection tubes should be **clearly labeled** with the patient's name, specimen ID and collection date. All specimens should be transported to the SLI **as soon as possible** for testing **within 24 hours of collection**. The MDPH epidemiologist (617-983-6800) can assist with arranging proper transport. **Prior to shipmen, specimens should be stored at 4°C and then shipped with ice packs.** The only exception would be to store and ship fixed tissues or tissue blocks at room temperature.

CONTROL MEASURES

Source control measures should be instituted for all patients who present to a health-care setting with fever and respiratory symptoms. Such patients should be managed with due attention to respiratory hygiene, cough etiquette and droplet precautions. They should also be questioned about recent travel history. Patients with suspected influenza A (H5N1) should **promptly** receive a neuraminidase inhibitor pending the results of diagnostic laboratory testing; see the section below on **Antiviral Medications** for further guidance**.**

CDC's current interim guidance for infection control of avian influenza can be found at: http://www.cdc.gov/flu/avian/professional/infect-control.htm. The World Health Organization (WHO) has issued interim infection control guidelines for health care facilities and a WHO consultation committee recently published an updated version of these recommendations, see: http://content.nejm.org/cgi/reprint/353/13/1374.pdf. The OSHA guidance on protecting employees including laboratory and healthcare providers from avian influenza can be found at: http://www.osha.gov/OshDoc/data_AvianFlu/avian_flu_guidance_english.pdf. The interim control measures

outlined below are based primarily on these three sources, plus the references listed at the end of this document.

A. Precautions in Healthcare Facilities

Isolation precautions should be implemented for all hospitalized patients diagnosed with, or under evaluation for, suspect avian influenza A (H5N1), as follows:

1. Standard Precautions

- ❑ Hand hygiene is absolutely essential
  - o Before and after all patient contact.
  - o As soon as possible after contact with items contaminated or potentially contaminated with respiratory secretions.

2. Contact Precautions

- ❑ Use gloves and gown for all patient contact.
- ❑ Use disposable equipment (blood pressure cuffs, thermometers) or equipment that can be disinfected before use with another patient (stethoscopes, etc.).

3. Droplet Precautions

- ❑ Wear goggles or face shields when within 3 feet of the patient.

Important considerations:

- o Face shields are insufficient protection for airborne hazards or for facial splashes.

4. Airborne Precautions

- ❑ Place the patient in an airborne infection isolation room
  - o Airborne infection isolation rooms should have monitored negative air pressure in relation to the corridor, with 6 to 12 air changes per hour, and
  - o should exhaust air directly to the outside or have re-circulated air filtered by a high efficiency particulate air (HEPA) filter.
- ❑ Keep the doors to the patient room closed; this protects other employees who are nearby.
- ❑ If an airborne infection isolation room is unavailable, contact the healthcare facility engineer to assist or use portable HEPA filters (see Environmental Infection Control Guidelines at www.cdc.gov/ncidod/hip/enviro/guide.htm) to augment the number of air changes per hour.
- ❑ Use a fit-tested respirator, at least as protective as a NIOSH-approved N-95 filtering face piece (i.e. disposable) respirator, when entering the room.

5. Transmission Prevention Strategies in Healthcare Settings

- ❑ Place patients that are AI-infected and those that are suspected of being AI-infected together in the same room if private rooms are not available. This would only be a likely scenario if there were a major avian influenza outbreak in your area.
- ❑ If possible, try not to place patients with seasonal influenza and those with AI in the same room. Although the risk is relatively small, the sharing of the same room by such patients would increase the chances of co-infection of patients with the two viruses and this could lead to viral reassortment of genes and the possible emergence of a novel human-adapted virus.
- ❑ Minimize transportation of influenza patients outside of room.
- ❑ Limit the number of health care workers caring for influenza patients.
- ❑ Limit the number of visitors to influenza patients.

Precautions should be continued for 14 days after onset of symptoms or until either an alternative diagnosis is established or diagnostic test results indicate the patient is not infected with influenza A virus. Children less than 12 years of age and those who are immunosuppressed may shed virus for longer periods of time and may need to remain on precautions for up to 21 days after onset of symptoms.

Low suspect avian influenza cases managed as outpatients and should be isolated in the home setting on the basis of principles outline for the home isolation of patients with severe acute respiratory syndrome (SARS) (see www.cdc.gov/ncidod/sars/guidance/i/pdf/i.pdf).

B. Vaccination of Health Care Workers

Currently, only 40% of health-care workers receive seasonal influenza vaccine. It is very important that all health-care workers involved in the care of patients with documented or suspected avian influenza be vaccinated with the most recent seasonal human influenza vaccine. In addition to providing protection against the predominant circulating influenza strains, this measure is intended to reduce the likelihood of a health-care worker's being co-infected with human and avian strains, resulting in possible genetic reassortment and the emergence of a potential novel human-adapted strain.

If a health-care worker is receiving influenza vaccine at the time of caring for a suspect avian influenza patient, use inactivated influenza vaccine rather than the live-attenuated influenza vaccine (LAIV), if possible. This will minimize the development of symptoms, which are a normal side effect of the live-attenuated vaccine, but could be confused with nosocomial transmission of avian influenza. In addition, recent administration of LAIV will make rapid diagnostic tests difficult to interpret.

C. Surveillance of Health Care Workers

1. Health care workers should be instructed to be vigilant for the development of fever, respiratory symptoms, and/or conjunctivitis (i.e., eye infections) for 10 days after last exposure to avian influenza-infected patients.
2. Health care workers who become ill should seek medical care and, prior to arrival, notify their health care providers that they may have been exposed to avian influenza. If an alternative cause is not identified, they should be treated immediately with oseltamivir on the assumption of influenza infection.
3. Employees should notify occupational health and infection control personnel at their facility of exposure and if they develop symptoms.
4. Health care workers who become ill should be advised to stay home until 24 hours after the resolution of fever, unless an alternative diagnosis is established or diagnostic tests are negative for influenza A virus. While at home, ill persons should practice good respiratory hygiene and cough etiquette (www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm) to lower the risk of transmission of virus to others.
5. Health care workers who have been exposed to infectious aerosols, secretions or other body fluids or excretions, due to a lapse in infection control, should be considered for postexposure prophylaxis with oseltamivir at a suggested dose for adults at 75 mg once daily for 7-10 days. Health care workers involved in high risk procedures (e.g., aerosol generating) should consider the need for preexposure prophylaxis. Please see the section below on **Antiviral Medications** for further guidance.
6. Health care workers caring for patients with avian influenza A (H5N1) should avoid caring for other patients.

For the most current infection control precautions for avian influenza A (H5N1), see: http://www.cdc.gov/flu/avian/professional/infect-control.htm.

D. Home Isolation/Precautions

Low suspect avian influenza cases can be managed as outpatients and should be isolated in the home setting on the basis of principles outlined for the home isolation of SARS patients. A few of the major recommendations include:

1. Patients should not leave the home for the duration of the isolation period, except as necessary for follow-up medical care. When movement outside the house is necessary, the patient should wear a mask and not use public transportation.
2. Separate the patient from others in the household to the extent possible. Use a separate room and bathroom, if available.
3. Household contacts should use appropriate hand hygiene, should not share utensils and should avoid face-to-face contact with suspected or proven cases. If they must have close contact with confirmed cases in their infectious period, they should consider using a respirator and eye protection.
4. Limit the number of persons in the household to those who are essential for patient support. Other household members should be relocated to minimize contact with the patient. This is particularly important for those at risk for complications.
5. Unexposed persons who do not have an essential need to be in the home should not visit.

For more complete guidance for the management of patients at home (including assessment of the residence to ensure it is suitable for home isolation), see http://www.cdc.gov/ncidod/sars/guidance/I/patients_home.htm.

E. Surveillance among Close Contacts of Patients with Avian Influenza A (H5N1)

Contacts who have shared a defined setting (household, extended family, hospital or other residential/military setting) with avian influenza A (H5N1) patients should be managed according to the principles outlined for contacts of patients with SARS. A few of the major recommendations include:

1. Household members and other close contacts of patients with known or suspect avian influenza A (H5N1) should be vigilant for fever (and measure their temperature twice a day) and/or respiratory symptoms (e.g., sore throat, cough, shortness of breath) for 10 days after their last exposure.
2. If household contacts develop fever or respiratory symptoms arrangements should be made immediately for a medical evaluation. In advance of the evaluation, healthcare providers should be informed that the person (and those who may accompany him or her) is a close contact of a case of avian influenza A (H5N1), so that arrangements can be made to prevent transmission to others in the healthcare setting. Household contacts with these symptoms should receive empiric treatment with oseltamivir.
3. Exposed contacts should take antiviral prophylaxis with oseltamivir at a suggested dose for adults at 75 mg once daily for 7-10 days. Please see the section below on **Antiviral Medications** for further guidance.
4. Symptomatic household contacts or other close contacts should follow the same precautions for recommended for those with avian influenza A (H5N1).
5. In the absence of fever or respiratory symptoms, household contact need not limit their activities outside the home.
6. Household contacts should be vaccinated with the most recent seasonal human influenza vaccine (use inactivated influenza vaccine rather than live-attenuated influenza vaccine, if possible).

For more complete guidance for the management of contacts of cases of avian influenza A (H5N1), see http://www.cdc.gov/ncidod/sars/guidance/I/patients_home.htm.

ANTIVIRAL MEDICATIONS

Patients with suspected avian influenza A (H5N1) should **promptly** receive a neuraminidase inhibitor pending the results of diagnostic laboratory testing. Exposed close contacts of confirmed (and highly suspect) cases should be started antiviral prophylaxis **immediately**. If there is a lower index of suspicion, antiviral prophylaxis can be deferred until laboratory confirmation is obtained or until there is any progression/deterioration in the clinical course of the individual with suspect avian influenza A (H5N1).

Health care workers who have been exposed to infectious aerosols, secretions or other body fluids or excretions, due to a lapse in infection control, should be considered for postexposure prophylaxis. Health care workers involved in high risk procedures (e.g., aerosol generating) should consider the need for preexposure prophylaxis.

There are two neuraminidase inhibitors licensed for use in the United States for the treatment and prophylaxis of both influenza A and B, zanamivir (Relenza®) and oseltamivir (Tamiflu®). The Food and Drug Administration recently extended chemoprophylaxis approval of oseltamivir to include adults and children ≥1 year of age. Zanamivir is now approved in the U.S. for treatment of individuals ≥7 years of age, and for chemoprophylaxis in individuals ≥5 years of age.

The optimal dose and duration for treatment and prophylaxis of avian influenza A (H5N1) with neuraminidase inhibitors are uncertain, and currently approved regimens likely represent the minimum required. The World Health Organization (WHO) has issued guidelines for the use of oseltamivir. To date, there has been no experience with the use of zanamivir in the treatment of avian influenza A. However, Zanamivir is mentioned by the WHO for consideration as an alternative drug (weak recommendation). Recommendations for the use of the neuraminidase inhibitors for the treatment and prophylaxis of avian influenza A in humans are outlined below.

Suggested Dosing Schedule of Oseltamivir for the Treatment and Prevention of Avian Influenza A (H5N1), According to Patient's Age[1,2]

Antiviral Drug	1-6 yrs	7-12 yrs	≥13 yrs
Treatment			
Oseltamivir [1,3]	**Weight** **≤15 kg:** 30 mg twice daily for 5 days; **>15-23 kg:** 45 mg twice daily for 5 days; **>23-40 kg:** 60 mg twice daily for 5 days; **>40kg:** 75 mg twice daily for 5 days (or longer)[3]	**Weight** **≤15 kg:** 30 mg twice daily for 5 days; **>15-23 kg:** 45 mg twice daily for 5 days; **>23-40 kg:** 60 mg twice daily for 5 days; **>40kg:** 75 mg twice daily for 5 days (or longer)[3]	75 mg twice daily for 7-10 days[3,4,5,6]
Prevention			
Oseltamivir [1,3]	**Weight** **≤15 kg:** 30 mg once daily for 5 days; **>15-23 kg:** 45 mg once daily for 5 days; **>23-40 kg:** 60 mg once daily for 5 days; **>40kg:** 75 mg once daily for 7-10 days[3]	**Weight** **≤15 kg:** 30 mg once daily for 5 days; **>15-23 kg:** 45 mg once daily for 5 days; **>23-40 kg:** 60 mg once daily for 5 days; **>40kg:** 75 mg once daily for 7-10 days[3]	75 mg once daily for 7-10 days (up to 6 wks)[3,4,5,6]

NA = not applicable

[1] The doses listed are those currently approved in the United States. The duration of prophylaxis with oseltamivir has been extended to be consistent with current WHO guidelines.

[2] To date, there has been no experience with the use of zanamivir in the treatment of avian influenza A.

[3] Loading doses, higher doses (150 mg twice daily in adults) and treatment for 7-10 days are considerations in treating severe infections. But, there is no empiric data suggesting they are helpful and prospective studies are needed. Increased doses and duration of treatment have been suggested as strategies to reduce the risk for development of drug resistance.

[4] For patients with hepatic disease, oseltamivir use has not been evaluated.

[5] For adults with renal failure, reduce dose if creatinine clearance is $\leq$ 30 mL/min; if creatinine clearance is 10-30 mL/min, 75 mg once daily. No oseltamivir regimen is available for patients with end-stage renal disease.

[6] For adults with renal failure, if creatinine clearance is 10-30 mL/min, 75 mg every other day. No oseltamivir regimen is available for patients with end-stage renal disease.

Sources:
WHO. WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. (May 2006) (http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/)
The Writing Committee of the World Health Organization (WHO) consultation on human influenza A/H5. Avian influenza A (H5N1) infection in humans. N Engl J Med 2005;353:1374-85. (http://content.nejm.org/cgi/reprint/353/13/1374.pdf)
CDC. Prevention and Control of Influenza. MMWR 2006;55(No. RR-10):1-48. (http://www.cdc.gov/mmwr/PDF/rr/rr5510.pdf)
Moscona, A. N Engl J Med 2005:353:1363-73. (http://content.nejm.org/cgi/reprint/353/13/1363.pdf)
Oseltamivir package insert (http://www.rocheusa.com/products/tamiflu/pi.pdf)

Please consult the CDC website for the latest recommendations for the use of antiviral agents for the treatment of avian influenza http://www.cdc.gov/flu/avian/professional/

GENERAL SEASONAL INFLUENZA VACCINATION INFORMATION

At present, a vaccine to protect humans from highly pathogenic avian influenza H5N1 strains has been liscenced but is not commercially available. It is recommended that healthcare workers and clinical laboratorians potentially involved in the care of patients or handling of specimens from patients with documented or suspected avian influenza should be vaccinated annually with the most recent **seasonal** human influenza vaccine. In addition to providing protection against the predominant circulating influenza strains, this measure is intended to reduce the likelihood of a healthcare worker or laboratorian being co-infected with both human and avian influenza viruses, where genetic reassortment could take place, leading to the emergence of a novel human-adapted strain. Vaccination efforts should also be directed at other groups at higher risk of co-infection, such as travelers, airline employees, U.S. citizens living abroad, poultry employees and animal handlers.

Following transition to a pandemic situation, information pertaining to the status of pandemic vaccine development will be disseminated to healthcare providers by public health officials as soon as it becomes available. For more information about the H5N1 vaccine development process, visit the National Institutes of Health website: http://www3.niaid.nih.gov/news/newsreleases/2005/avianfluvax.htm.

Important considerations: Influenza vaccination of U.S. healthcare workers remains below 40% despite the vaccine's safety and effectiveness. A recent publication clearly describes the benefits of yearly influenza vaccination of healthcare workers. Yearly influenza vaccination of healthcare workers has been demonstrated to reduce absenteeism, nosocomial influenza transmission, and the associated economic losses and disruption of routine operations.

ADVICE FOR TRAVELERS

1. Travelers to areas affected by avian influenza A (H5N1) should be immunized with the most current trivalent human influenza vaccine, preferably at least 2 weeks before traveling.
2. Travelers should avoid direct contact with poultry, including chickens, ducks, or geese that appear well, and farms or live animal markets with poultry, or other places where live poultry are raised or kept, and they should avoid touching surfaces contaminated with poultry droppings or secretions.
3. Travelers should reduce possible exposure by practicing good hand hygiene, with frequent hand washing or use of alcohol hand gels.
4. Undercooked eggs or other foods from poultry should not be eaten. Eggs should be washed in warm soapy water before handling and cooking. The cooking temperature for poultry and poultry products (including eggs) should reach 165 °F (74°C).
5. Travelers should monitor themselves for 10 days upon return from an affected area. If they become ill with fever, sore throat or trouble breathing, they should consult a health care provider. Before visiting a healthcare setting, they should tell their provider: 1) their symptoms, 2) where they traveled, and 3) if they had direct contact with poultry or a severely ill person.
6. When seeing ill travelers after return from affected areas, providers need to ensure that appropriate arrangements can be made to prevent transmission to others in the healthcare setting.

EDUCATIONAL RESOURCES FOR PATIENTS AND PROVIDERS

Patient-specific:

1. General information about avian influenza: http://www.cdc.gov/flu/avian/
2. CDC Key Facts About Avian Influenza (Bird Flu) and Avian Influenza A (H5N1) Virus: http://www.cdc.gov/flu/avian/gen-info/facts.htm
3. How to protect you and your loved ones against the flu, avian flu (bird flu) and other colds and cough illnesses (available in 9 languages): http://www.mass.gov/dph/cdc/epii/flu/flufacts.htm
4. Advice for travelers: http://www.cdc.gov/travel/other/avian_influenza_se_asia_2005.htm
5. MDPH Handwashing materials for the public: http://www.mass.gov/dph/cdc/handwashing/hw.htm#general
6. CDC Cover Your Cough posters: http://www.cdc.gov/flu/protect/covercough.htm

Provider-specific:

1. Avian influenza: Resources for Health Professionals: http://www.cdc.gov/flu/avian/professional/
2. WHO Avian influenza Frequently Asked Questions: http://www.who.int/csr/disease/avian_influenza/avian_faqs/en/index.html
3. For more information about the avian influenza outbreaks in Asia and Europe (including case counts): http://www.who.int/csr/disease/avian_influenza/en/
4. For more information about infection among poultry and animals in Asia and Europe: http://www.oie.int/eng/en_index.htm
5. Interim guidance for the use of masks to control influenza transmission: http://www.cdc.gov/flu/professionals/infectioncontrol/maskguidance.htm
6. MDPH avian influenza information: http://www.mass.gov/dph/cdc/epii/flu/avian_flu.htm
7. MDPH Handwashing materials for providers: http://www.mass.gov/dph/cdc/handwashing/hw.htm#health
8. Information about pandemic influenza and the HHS Pandemic influenza Plan: http://www.hhs.gov/pandemicflu/

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Influenza Vaccination of Health Care Personnel. MMWR 2006;55(No. RR-02). http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5502a1.htm
2. Centers for Disease Control and Prevention (CDC). Health Alert Update: Interim Guidance for Laboratory Testing and Surveillance. June 2006. http://www2a.cdc.gov/han/ArchiveSys/ViewMsgV.asp?AlertNum=00246
3. Centers for Disease Control and Prevention (CDC). Prevention and Control of Influenza. MMWR 2006;55 (No. RR-10). (http://www.cdc.gov/mmwr/PDF/rr/rr5510.pdf)
4. Centers for Disease Control and Prevention (CDC). Severe Acute Respiratory Syndrome. Supplement I: Infection Control in Healthcare, Home and Community Settings:1-28. (http://www.cdc.gov/ncidod/sars/guidance/i/pdf/i.pdf)
5. Kandun, I N, et. al. Three Indonesian Clusters of H5N1 Virus Infection in 2005. N Eng J Med 2006:355:2186-94. http://content.nejm.org/cgi/reprint/355/21/2186.pdf
6. Moscona, A. Neuraminidase Inhibitors for Influenza. N Engl J Med 2005;353:1363-73. (http://content.nejm.org/cgi/reprint/353/13/1363.pdf)
7. Occupational Safety and Health Administration (OSHA). OSHA Guidance Update on Protecting Employees from Avian Flu (Avian Influenza) Viruses. 2006:1-71. (http://www.osha.gov/OshDoc/data_AvianFlu/avian_flu_guidance_english.pdf)
8. Oner, A F et. al. Avian Influenza A (H5N1) Infection in Eastern Turkey in 2006. N Eng J Med 2006:355:2179-85. http://content.nejm.org/cgi/reprint/355/21/2179.pdf
9. Oseltamivir package insert (http://www.rocheusa.com/products/tamiflu/pi.pdf)
10. Relenza® (Zanamivir) package insert. (http://us.gsk.com/products/assets/us_relenza.pdf)
11. Tamiflu® (oseltamivir phosphate) package insert. (http://www.rocheusa.com/products/tamiflu/pi.pdf)
12. Webster, R G, and Govorkova, E A. H5N1 Influenza- Continuing Evolution and Spread. N Eng J Med 2006:355:2174-77. http://content.nejm.org/cgi/reprint/355/21/2174.pdf
13. World Health Organization (WHO). Collecting, preserving and shipping specimens for the diagnosis of avian influenza A(H5N1) virus infection. Guide for Field Operations. October 2006:1-80. (http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_ARO_2006_1/en/index.html)
14. World Health Organization (WHO). Influenza A (H5N1): WHO interim infection control guidelines for health care facilities:1-31. (http://www.who.int/csr/disease/avian_influenza/guidelines/Guidelines_for_health_care_facilities.pdf)
15. World Health Organization (WHO). WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. (May 2006). (http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/)
16. Writing Committee of the World Health Organization (WHO) consultation on human influenza A/H5. Avian influenza A (H5N1) infection in humans. N Engl J Med 2005;353:1374-85. (http://content.nejm.org/cgi/reprint/353/13/1374.pdf)
17. U.S. Food and Drug Administration website. Product Approval Information on Influenza Virus Vaccine, H5N1. http://www.fda.gov/cber/products/h5n1san041707.htm

CHECKLIST: STRATEGIES TO PREVENT AVIAN INFLUENZA VIRUS INFECTION IN A NON-PANDEMIC SETTING

Isolation precautions in health care facilities:

Standard Precautions

- ❑ Wash hands carefully for 15-20 seconds before and after all patient contact, or contact with surfaces potentially contaminated with respiratory secretions.

Contact Precautions

- ❑ Use gloves and gown for all patient contacts.
- ❑ Use disposable equipment (blood pressure cuffs, thermometers) or equipment that can be disinfected before use with another patient (eg, stethoscopes).

Droplet Precautions

- ❑ Wear goggles/face shields within 3 feet of the patient.

Airborne Precautions

- ❑ The patient should be placed in an airborne infection isolation room.
- ❑ If such a room is unavailable, portable HEPA filters should be used.
- ❑ Use at least a disposable N95 respirator when in the isolation room or other room containing the patient and especially when engaged in high-risk aerosol generating procedures.

Transmission Prevention Strategies

- ❑ Group infected patients in the same room if private rooms are not available.
- ❑ Minimize transportation of influenza patients outside of room.
- ❑ Limit the number of employees caring for influenza patients.
- ❑ Limit the number of visitors to influenza patients.

Additional Guidance

- ❑ Get the seasonal influenza vaccine.
- ❑ If you develop flu-like symptoms, stay at home except to get medical attention.
- ❑ Avian and human influenza symptoms are similar.

Health care worker exposures:

- ❑ Health care workers involved in high-risk procedures (e.g., aerosol generating) should consider the need for pre-exposure prophylaxis.
- ❑ Health care workers should be instructed to be vigilant for the development of fever, respiratory symptoms, and/or conjunctivitis (i.e., eye infections) for 10 days after last exposure to avian influenza infected patients.
- ❑ Health care workers who become ill should seek medical care and, prior to arrival, notify their health care providers that they may have been exposed to avian influenza. If an alternative cause is not identified, they should be treated immediately with oseltamivir on the assumption of influenza infection.
- ❑ Employees should notify occupational health and infection control personnel at their facility of exposure and if they develop symptoms.
- ❑ Health care workers who become ill should be advised to stay home until 24 hours after the resolution of fever, unless an alternative diagnosis is established or diagnostic tests are negative for influenza A virus. While at home, ill persons should practice good respiratory hygiene and cough etiquette (www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm) to lower the risk of transmission of virus to others.
- ❑ Health care workers who have been exposed to infectious aerosols, secretions or other body fluids or excretions, due to a lapse in infection control technique, should be considered for postexposure prophylaxis with oseltamivir at a suggested dose for adults at 75 mg once daily for 7-10 days.
- ❑ Health care workers caring for patients with avian influenza A (H5N1) should avoid caring for other patients.

CHECKLIST: STRATEGIES TO PREVENT AVIAN INFLUENZA VIRUS INFECTION IN A NON-PANDEMIC SETTING

Precautions for household and close contacts:

- ❑ Household contacts should use appropriate hand hygiene (washing for 20 seconds with soap and water), should not share utensils and should avoid face-to-face contact with suspected or proven cases
- ❑ Cover your mouth when you cough or sneeze. Cough or sneeze into a tissue or the inside of your elbow. Throw tissues away and wash your hands.
- ❑ Separate the patient from others in the household to the extent possible. Use a separate room and bathroom, if available.
- ❑ Limit the number of persons in the household to those who are essential for patient support. Other household members should be relocated to minimize contact with the patient. This is particularly important for those at risk for complications.
- ❑ Contacts who have a defined setting (household, extended family, hospital or other residential institution, or military service) with a patient with proven or suspected avian influenza (H5N1) infection should monitor their own temperature twice daily and check for symptoms for 10 days after their last exposure.

Precautions for travelers:

- ❑ Travelers to areas affected by avian influenza A (H5N1) should be immunized with the most current trivalent human influenza vaccine, preferably at least 2 weeks before traveling.
- ❑ Travelers should avoid direct contact with poultry, including chickens, ducks, or geese that appear well, and farms or live animal markets with poultry, and they should avoid touching surfaces contaminated with poultry droppings or secretions.
- ❑ Travelers should reduce possible exposure by practicing good hand hygiene, with frequent hand washing or use of alcohol hand gels.
- ❑ Undercooked eggs or other foods from poultry should not be eaten. Eggs should be washed in warm soapy water before handling and cooking. The cooking temperature for poultry and poultry products (including eggs) should reach 165 °F (74°C). Travelers should monitor themselves for 10 days upon return from an affected area. If they become ill with fever, sore throat or trouble breathing, they should consult a health care provider. Before visiting a healthcare setting, they should tell their provider: 1) their symptoms; 2) where they traveled; and 3) if they had direct contact with poultry or a severely ill person.
- ❑ When seeing ill travelers after return from affected areas, providers need to ensure that appropriate arrangements can be made to prevent transmission to others in the healthcare setting.